One-Year Mission & Twins Study

J.B. Charles, Ph.D.

HRP IWS

February 8, 2016

time.com/meet-the-twins-unlocking-the-secrets-of-space/

The One-Year Mission

ISS Crew: Scott Kelly, Mikhail Kornienko Sign On For One-Year Mission

Posted: 11/26/2012 9:29 am EST Updated: 11/26/2012 9:40 am EST

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FOLLOW: Video, Scott Kelly, International Space Station, Iss Crew, Iss Mission, Mikhail Kornienko, International Space Station, Science News

By: Tariq Malik
Published: 11/26/2012 08:12 AM EST on SPACE.com

A veteran NASA space commander and Russian cosmonaut have signed on for the ultimate space voyage: a yearlong trip on the International Space Station.

American astronaut Scott Kelly and Russian cosmonaut Mikhail Kornienko will launch on the one-year space station flight in spring 2015 and return to Earth in spring 2016, NASA officials announced today (Nov. 26). They will begin their mission training in early 2013.

The mission will help NASA understand how the human body adapts to extremely long space missions, such as voyages around the moon, to an asteroid and ultimately to Mars, NASA officials said.

HOME > SCIENCE

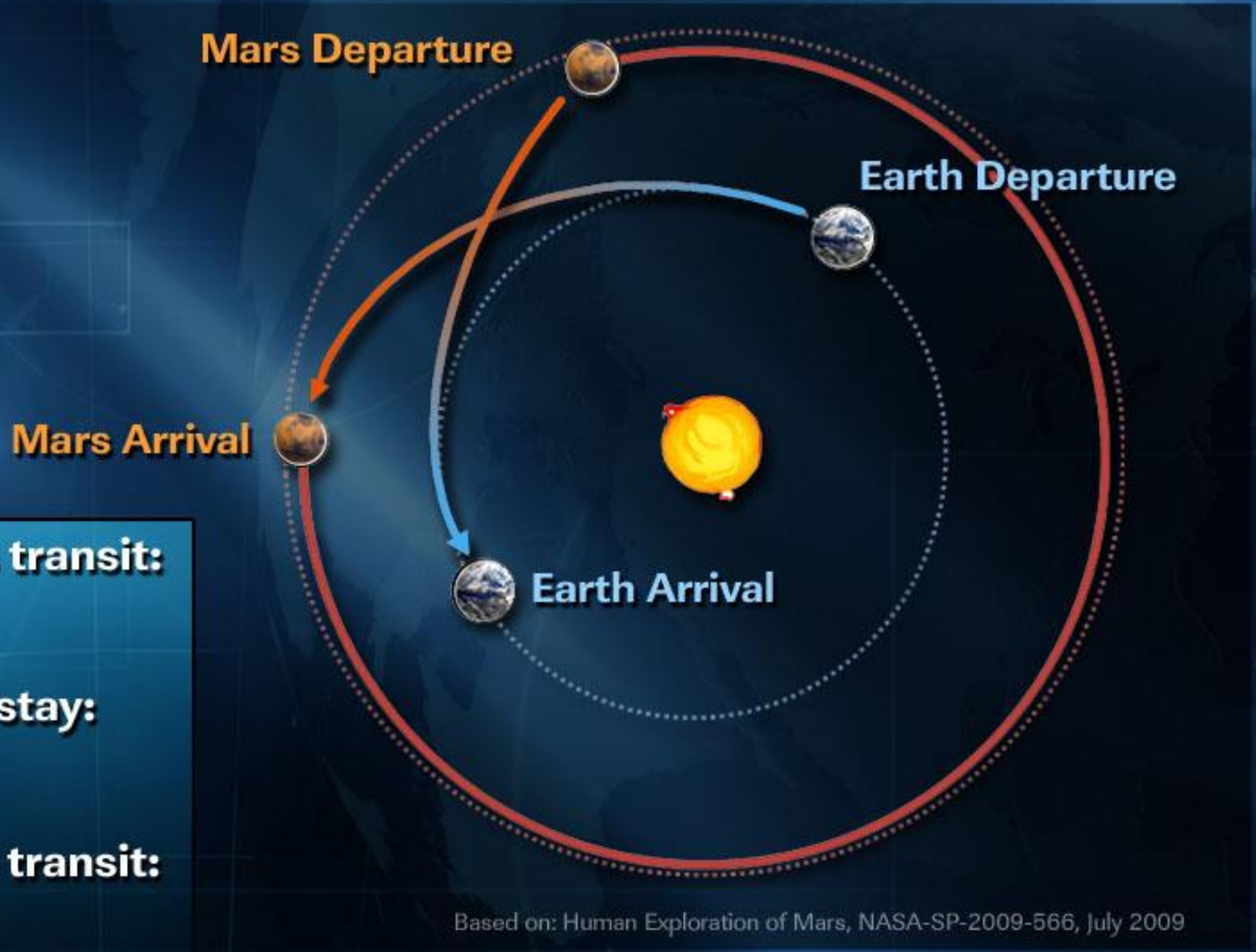
Astronaut Scott Kelly Preparing for Unprecedented One Year in Space; Mission to Experiment on His Bone Mass, Vision, Immune System

By Latin Times Staff Writer, Dec 07, 2012 08:00 PM EST

0 Comments | Like 0 | Tweet 0 | +1 0 | Share | Text Size − +

Tags: NASA, Space

Generic 900-day Astronaut Expedition to Mars



Earth-to-Mars transit:
~6 months

Mars surface stay:
~18 months

Mars-to-Earth transit:
~6 months

Human Research Objectives for One-Year ISS Mission (simplified)

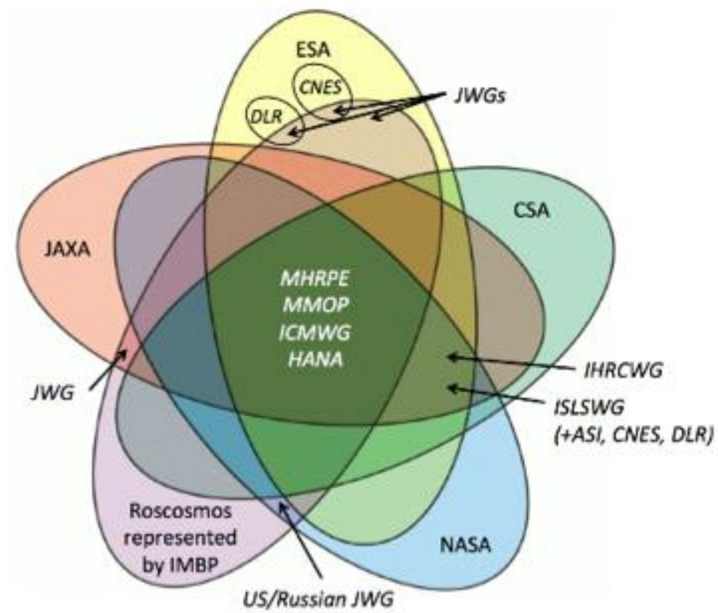
Are we as smart as we think we are based on 15 years of 6±-month ISS expeditions?

- **Previous Russian experience shows no "brick walls" out to 14 months**
- **Crewmember safety, health and efficiency on 30-month Mars round-trip missions will need "countermeasures" developed and tested on ISS**
  - ❖ How to extrapolate from 6 months to 30 months?
    - Year-long expedition permits next-step longer evaluation under controlled circumstances

Multilateral Human Research Panel for Exploration (MHRPE)

- Created by ISS Expert Working Group, Sep. 2011
- **Chartered by Space Station Control Board, Oct. 2013**
- Tasked to facilitate multilateral in-flight investigations
  - <u>All</u> remaining ISS increments
  - Starting with 2015 one-year mission (1YM) as demonstration

MHRPE Agency Leads	
NASA	**J. Charles**
CSA	**P. Johnson-Green**
ESA	**J. Ngo-Anh**
FSA	**V. Bogomolov**, V. Pochuev
JAXA	**S. Furukawa**



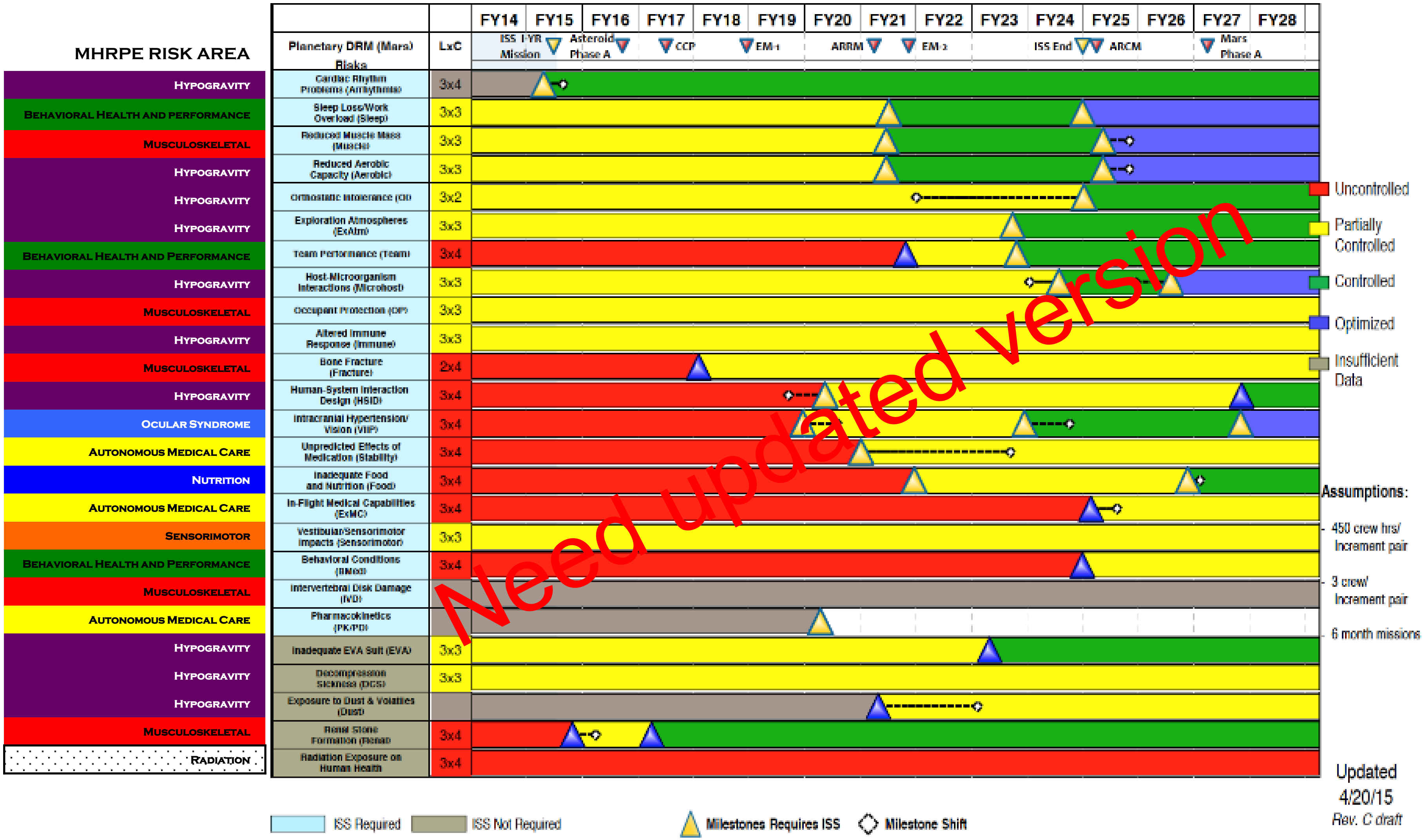
Human Research Objectives for 1YM

- **Utilize ISS efficiently to reduce human risks of exploration missions beyond low Earth orbit**
  - ❖ Implement a Year-long Expedition by two crewmembers (1 American, 1 Russian)
    - Demonstrate benefits of joint work using multilateral capabilities and resources on ISS
      - Extend earlier Russian work
    - Assess problems of joint work: scientific, training, scheduling, certification and implementation
  - ❖ **Apply experience to human risk reduction research on subsequent ISS missions of all durations**

Human Health and Performance Exploration Risks Across All Partners to be addressed by ISS Research

Risk Area
Musculoskeletal: Long-Term health risk of Early Onset Osteoporosis. Mission risk of reduced muscle strength and aerobic capacity
Sensorimotor: Mission risk of sensory changes or dysfunctions
Autonomous Medical Care: Mission and long-term health risk due to inability to provide adequate medical care throughout the mission (Includes onboard training, diagnosis, treatment, and presence/absence of onboard physician)
Behavioral Health and Performance: Mission and long-term behavioral health risk.
Ocular Syndrome: Mission and long-term health risk of Microgravity-Induced Visual Impairment and/or elevated Intracranial Pressure (VIIP)
Nutrition: Mission risk of behavioral and nutritional health due to inability to provide appropriate quantity, quality and variety of food
Hypogravity: Long-term risk associated with adaptation during IVA and EVA on the Moon, asteroids, Mars (vestibular and performance dysfunctions) and postflight rehabilitation
Radiation: Long-term risk of carcinogenesis and degenerative tissue disease due to radiation exposure – **Largely addressed with ground-based research**

Mapping MHRPE Risk Areas to HRP Integrated Path to Risk Reduction



Three Major Areas of Biomedical Concern for Long Missions

- **Medical events**
  - Establish likelihood of negative events which change over time
  - Characterize response of known medical conditions
- **Physiological deconditioning**
  - **Establish efficacy of countermeasures for missions longer than ISS**
- **Behavior & Performance**
  - Characterize trends over time
  - Validate countermeasures

1YM Implementation Overview

Multilateral biomedical investigations on US and Russian crewmembers

2012

- **Agency-level bilateral agreement. Candidate investigations exchanged**

2013

- Developed milestones, overarching principles for hardware & data sharing, cross-participation
- Field Test experiment (joint, pre/post flight) initiated, transitioned to operations
- Fluid Shifts experiment (joint, in-flight) initiated; implementation issues identified, resolved
- Identified complementary ESA, JAXA, CSA investigations (thus “multilateral”)

2014

- Completed informed consent for US investigations for both crewmembers
- Crew time issues in work
- Data Sharing Principles signed by SSCB
- Initiated preflight baseline data collection and crewmember training
- Bilateral PI meetings for collaborations, data exchange needs
- **Initiated Twins Study**


2015

- Completed preparations for NASA Twins Study
- Completed informed consent for Russian investigations, baseline data collection, training
- Finalized documentation for joint investigations implementation under guidance of KNTS/Soloviev
- Resolved NASA crew time issues for Increments 45-46 (1YM, 2nd half)
- Launched March 27, 2015! Landing planned March 2, 2016
- *February 8 is flight day 318—23 to go!*
- Future year-long missions under discussion


Multilateral Biomedical Science Plan for 1YM

MHRPE Risk	Category	NASA	Roscosmos	JAXA	ESA	CSA
Sensorimotor & Musculoskeletal	Functional Capacity	***Field Test*** ***Functional Task Test* [D]**	***Effektivnost* [D]**			
	Physical Performance	**Sprint (control) ~~[D]~~** ***Hip QCT* [D]**	**Korrektsia** **[EDOS]/Motokard [D]** **Profilaktika [D]**		**EDOS** **[Korrektsia]** **[D]**	
Sensorimotor & Hypogravity	Human Factors	**Fine Motor Skills** **Habitability** **Training Retention**	Russian crewmember, GCTC collaborator			
Hypogravity	Metabolism	**Biochemical Profile~~[D]~~** **CardiOx ~~[D]~~** **Salivary Markers [D]**	**Morze [D]** **Neyroimmunitet [D]**		**Immuno-2** **[D]**	**TBD [D]**
	Microbial	**Microbiome**		**Myco**		
Behavioral Health & Performance	Behavioral Health	**Cognition** **Sleep Monitoring** **Reaction Self Test** **Journals [D]** **Neuromapping ~~[D]~~**	**Pilot-T** **Interactions-2** **Content**	**Biological Rhythms (48 Hours)**		
Ocular Syndrome	Visual Impairment	**Fluid Shifts** **Ocular Health/MedB1.10**		**IPVI**	~~**Energy**~~	

- Participation: **US astronaut**, **Russian cosmonaut**
- *Pre/postflight only*
- Korrektsia (Roscosmos) is same as EDOS (ESA)
- "Energy" NASA subject lost due to experiment BDC technical failure
- Unilateral investigations not shown

- Bilateral NASA, Roscosmos investigations
  - **Common ("joint")**
  - **Cross-participation**
  - [D] data-exchange only

Also done by Scott Kelly on previous 6-month expedition

Summary of investigation operations (weeks 1-13)

1YM Operations Summary

Inc 43:
Kor: M. Kornienko
Kel: S. Kelly

	Week	1	2	3	4	5	6	7	8	9	10	11	12	13
	Start Date	**9-Mar**	**16-Mar**	**23-Mar**	**30-Mar**	**6-Apr**	**13-Apr**	**20-Apr**	**27-Apr**	**4-May**	**11-May**	**18-May**	**25-May**	**1-Jun**
	EXPERIMENTS/ACTIVITIES													
NASA	Salivary Markers				Kel					Kel				Kel
	Microbiome				Kel	Kel				Kel				Kel
	Journals					Kel	Kel			Kel?	Kel?			
	Biochemical Profile					Kel								
	Ocular Health				Kor, Kel		Kor	Kor	Kel					
	Cognition				Kor	Kel				Kor	Kel			
	Sleep			Kor, Kel	Kor, Kel			Kor, Kel			Kor, Kel	Koe, Kel		Kor, Kel
	Fine Motor skills			Kor, Kel	Kor, Kel	Kor, Kel	Kor, Kel	Kor, Kel	Kor, Kel	Kor, Kel	Kor, Kel	Kor, Kel	Kor, Kel	Kor, Kel
	Habitability				Kel		Kel							
	Reaction Self Test				Kor, Kel		Kor, Kel		Kor, Kel		Kor, Kel		Kor, Kel	
	Cardio Ox					Kel								
	Sprint					Kel			Kel					
	Neuromapping						Kel							
	Twins Study					Kel				Kel				Kel
	Fluid Shifts											Kor, Kel	Kor, Kel	Kor, Kel
RSA	Interactions-2					Kel				Kel		Kel		Kor, Kel
	Pilot-T													
	Content													
	Morze													
	Korrektsia													
	Profilaktika													
	Neyroimmunitet													
JAXA	Myco							Kel						
	Biological Rhythms						Kel							
	IPVI													
ESA	Energy													
	Immuno-2													
	EDOS													

Summary of investigation operations (weeks 14-26)

1YM Operations Summary

Inc 43:
Kor: M. Kornienko
Kel: S. Kelly

Agency	Week	14	15	16	17	18	19	20	21	22	23	24	25	26
	Start Date	8-Jun	15-Jun	22-Jun	29-Jun	6-Jul	13-Jul	20-Jul	27-Jul	3-Aug	10-Aug	17-Aug	24-Aug	31-Aug
	EXPERIMENTS/ACTIVITIES													
NASA	Salivary Markers	Kel							Kel					
NASA	Microbiome	Kel		Kel					Kel					Kel
NASA	Journals		Kel?	Kel?	Kel	Kel	Kel	Kel	Kel	Kel	Kel	Kel	Kel	Kel
NASA	Biochemical Profile	Kel							Kel					
NASA	Ocular Health		Kor, Kel									Kor, Kel		
NASA	Cognition	Kor, Kel					Kor		Kel			Kor	Kel	
NASA	Sleep			Kor, Kel	Kel		Kor, Kel			Kor, Kel			Kor, Kel	Kor, Kel
NASA	Fine Motor skills	Kor, Kel	Kor, Kel	Kor, Kel		Kor, Kel		Kor, Kel		Kor, Kel		Kor, Kel		Kor, Kel
NASA	Habitability			Kel	Kel	Kel		Kel	Kel	Kel	Kel	Kel		Kel
NASA	Reaction Self Test	Kor, Kel		Kor, Kel		Kor, Kel	Kor, Kel	Kor, Kel	Kel	Kor	Kor, Kel		Kor, Kel	Kor, Kel
NASA	Cardio Ox	Kel												
NASA	Sprint	Kel		Kel			Kel	Kel			Kel		Kel	Kel
NASA	Neuromapping		Kel											Kel
NASA	Twins Study	Kel							Kel					
	Fluid Shifts											Kel	Kor	Kor, Kel
RSA	Interactions-2		Kor, Kel		Kor, Kel		Kor, Kel		Kor, Kel		Kor, Kel		Kel	
RSA	Pilot-T						Kor, Kel			Kor		Kor, Kel		
RSA	Content	Kor		Kor		Kor		Kor		Kor		Kor		
RSA	Morze								Kor					
RSA	Korrektsia								Kor					
RSA	Profilaktika													
RSA	Neyroimmunitet								Kor					
JAXA	Myco									Kel				
JAXA	Biological Rhythms									Kel	Kel?	Kel		Kel
JAXA	IPVI													
ESA	Energy													
ESA	Immuno-2													
ESA	EDOS													

Summary of investigation operations (weeks 27-28)

1YM Operations Summary														
	Week	(1) 27	(2) 28	(3) 29	30	31	32	33	34	35	36	37	38	39
	Start Date	7-Sep	14-Sep	21-Sep	28-Sep	5-Oct	12-Oct	19-Oct	26-Oct	2-Nov	9-Nov	16-Nov	23-Nov	30-Nov
NASA	**EXPERIMENTS/ACTIVITIES**													
	Salivary Markers													
	Microbiome	Kel	Kel											
	Journals	Kel	Kel											
	Biochemical Profile													
	Ocular Health													
	Cognition		Kor											
	Sleep	Kor, Kel	Kor, Kel											
	Fine Motor skills		Kor, Kel											
	Habitability	Kel	Kel											
	Reaction Self Test		Kor, Kel											
	Cardio Ox													
	Sprint													
	Neuromapping													
	Twins Study	Kel												
	Fluid Shifts		Kor, Kel											
RSA	Interactions-2	Kel												
	Pilot-T		Kel											
	Content													
	Morze													
	Korrektsia													
	Profilaktika													
	Neyroimmunitet													
JAXA	Myco													
	Biological Rhythms		Kel*											
	IPVI													
ESA	Immuno-2													
	EDOS													
	* partial data collection													

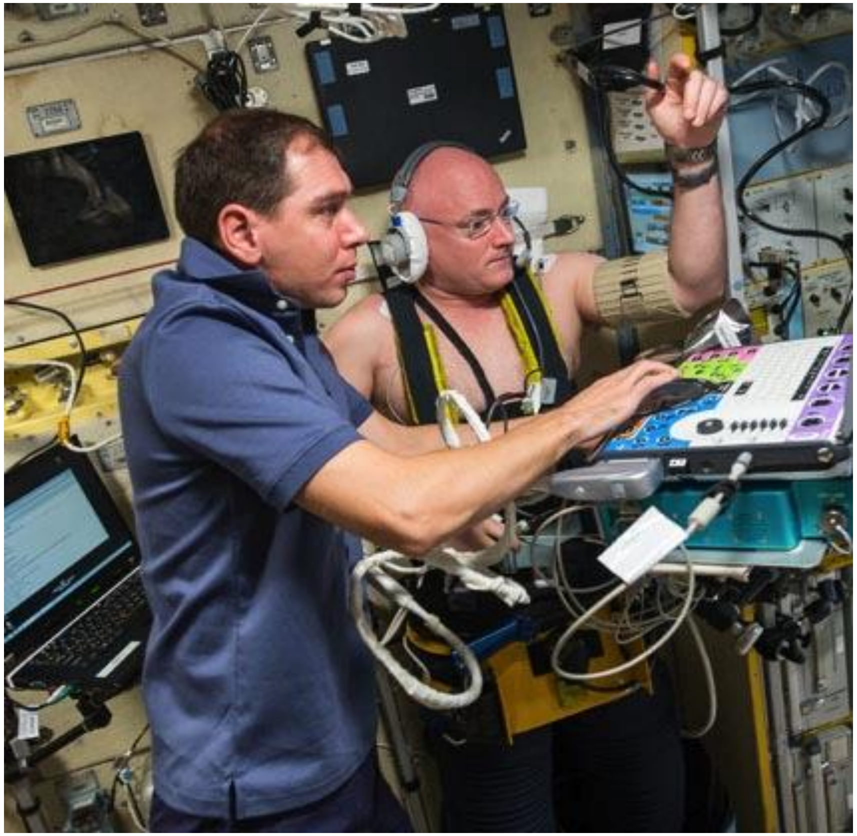
Inc 45:
Kor: M. Kornienko
Kel: S. Kelly

Fluid Shifts Investigation

M. Stenger (NASA), A. Hargens (UCSD), S. Dulchavsky (HFH), I. Alferova (RAS IBMP)

June 2015

September 2015



1YM Progress

Field Test at landing with Padalka

- ✓ Pilot Field Test concluded
- ✓ Padalka: 879 days in space

Twins Study

- Influenza vaccination
  - ✓ Scott Kelly on ISS, September 24
  - ✓ Mark Kelly in Houston, October 3

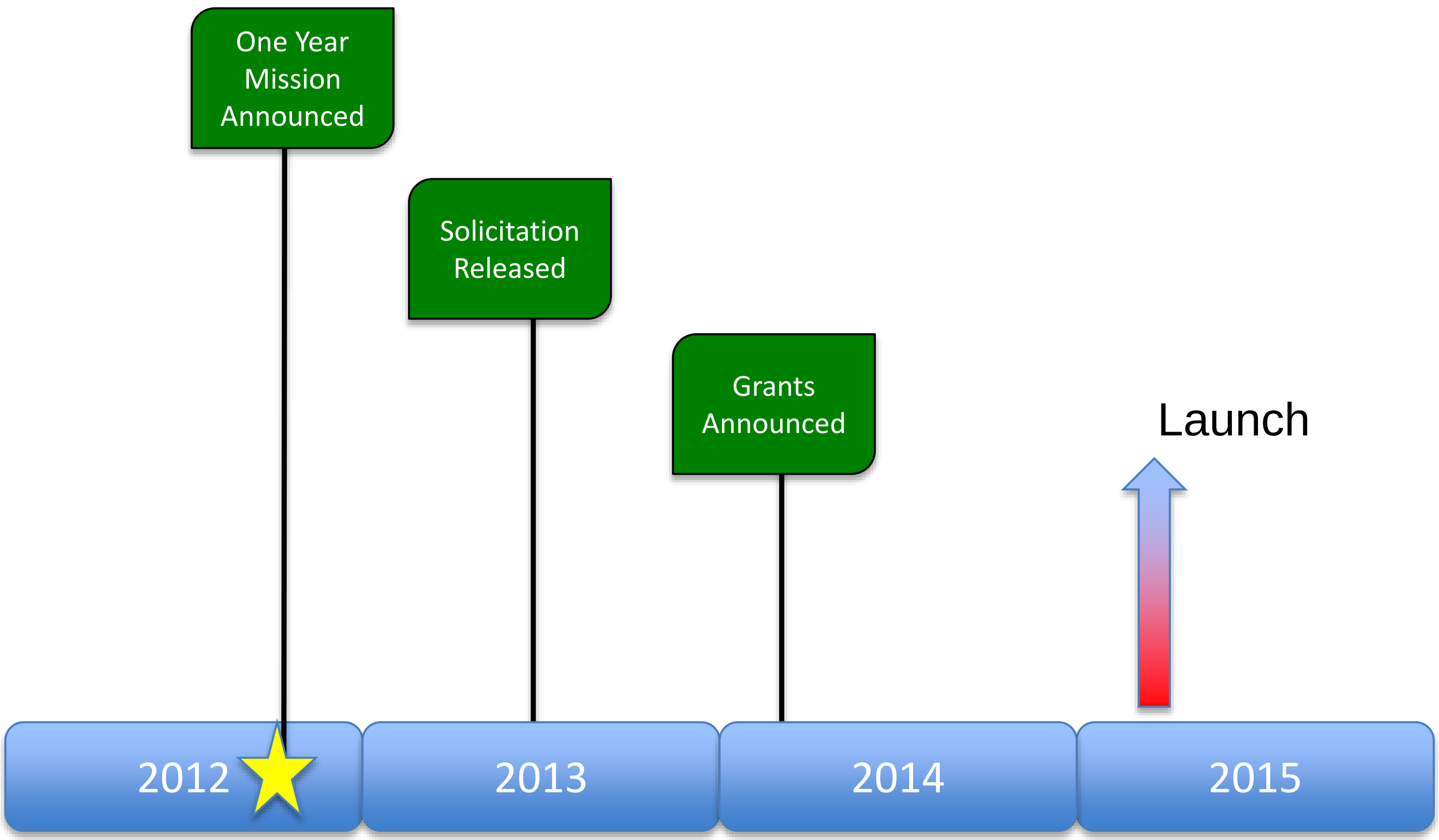
MHRPE 2.0

- **Apply lessons learned from bilateral 1YM to <u>all</u> future expeditions**
  - ❖ Compile and maintain Multilateral Investigations List (formerly "international fly-off plan") for future ISS complements
  - ❖ Recommend Integrated Multilateral Investigations (truly joint studies) to implementing organizations no fewer than 20 months before first required flight
  - ❖ Facilitate sharing of ISS and related results among relevant partner investigators and between research and medical communities
    - Encourage MHRPE Partner Agencies to endorse, support data sharing system management
  - ❖ Facilitate sharing, collaboration and consolidation of hardware, instrumentation and protocols across MHRPE Partners
  - ❖ Require active participation by all interested MHRPE Partner Agencies
  - ❖ **Encourage ISS Partner Agencies to streamline Implementation process**
    - **Simplify, reduce and standardize required documentation**
      - **Consolidate documentation across partners as much as possible**
    - **Establish bilateral (USOS-ROS) schedules**
    - **Identify and standardize approval processes**

National Aeronatics and Space Administration

www.nasa.gov/content/twins-study

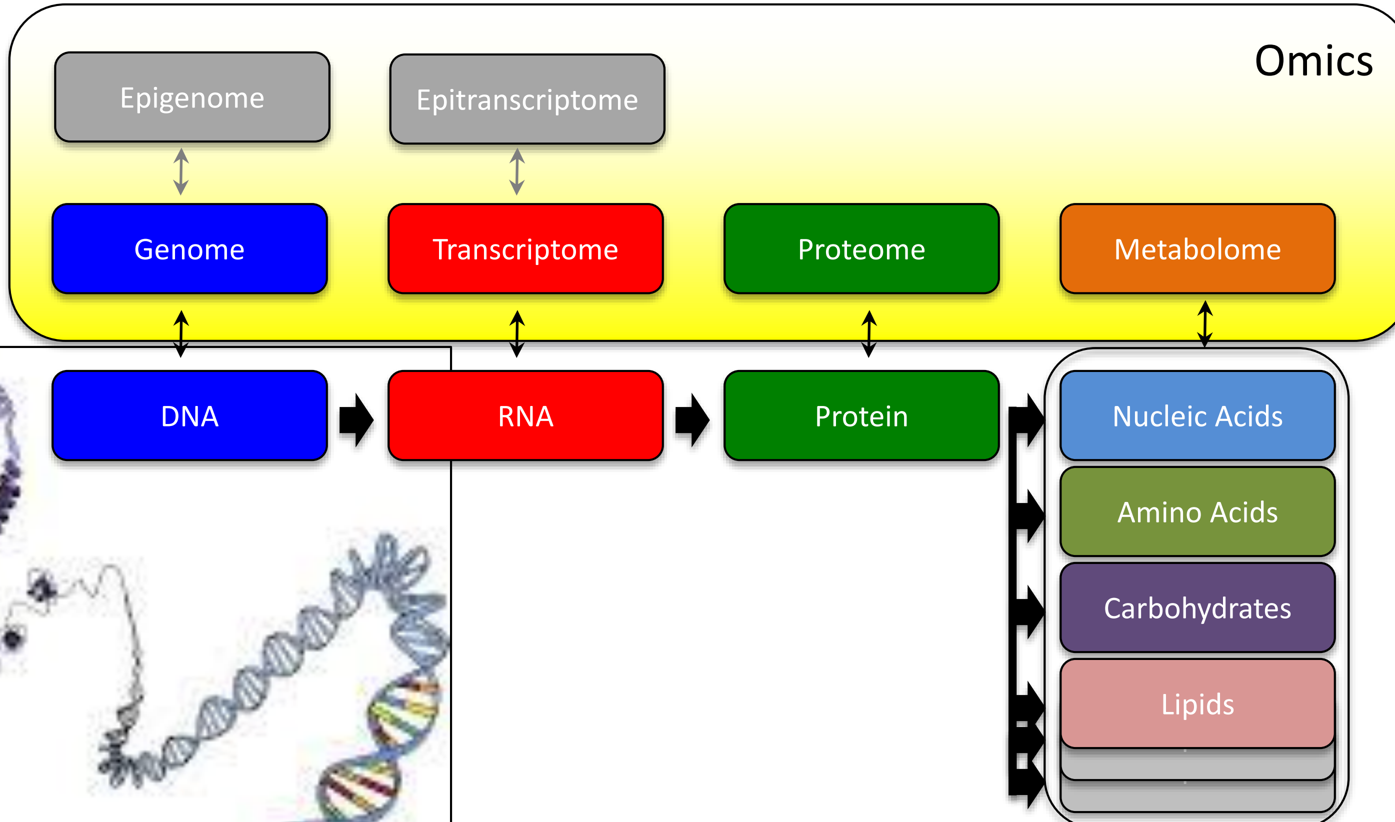
Too Late?

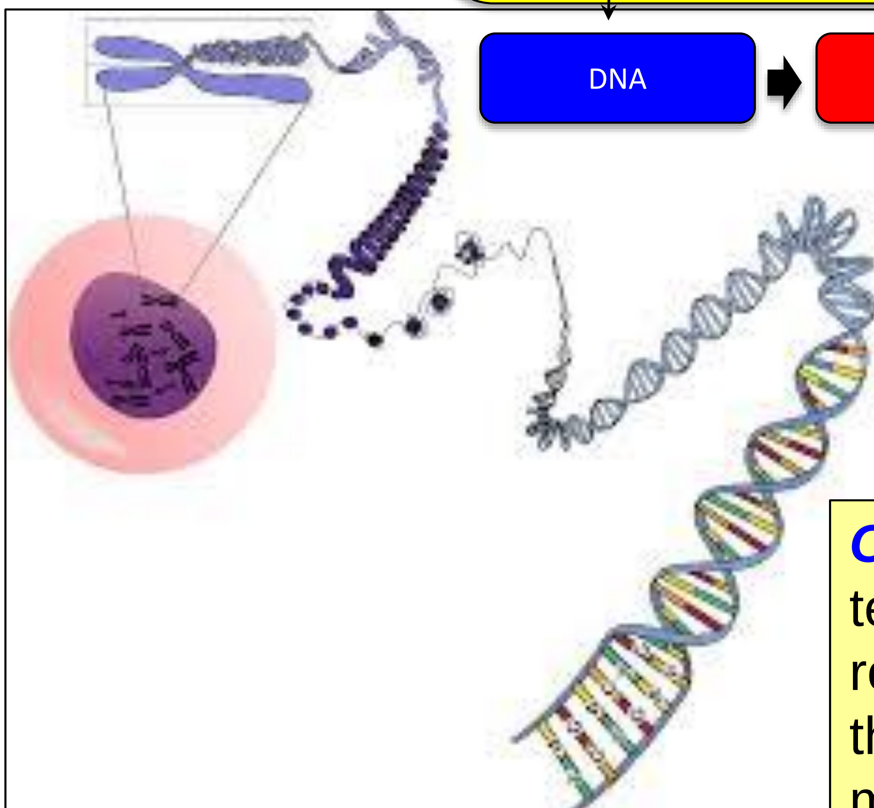


One Year Mission Announced
Solicitation Released
Grants Announced
Launch
2012
2013
2014
2015

A Chance in a Lifetime Opportunity?

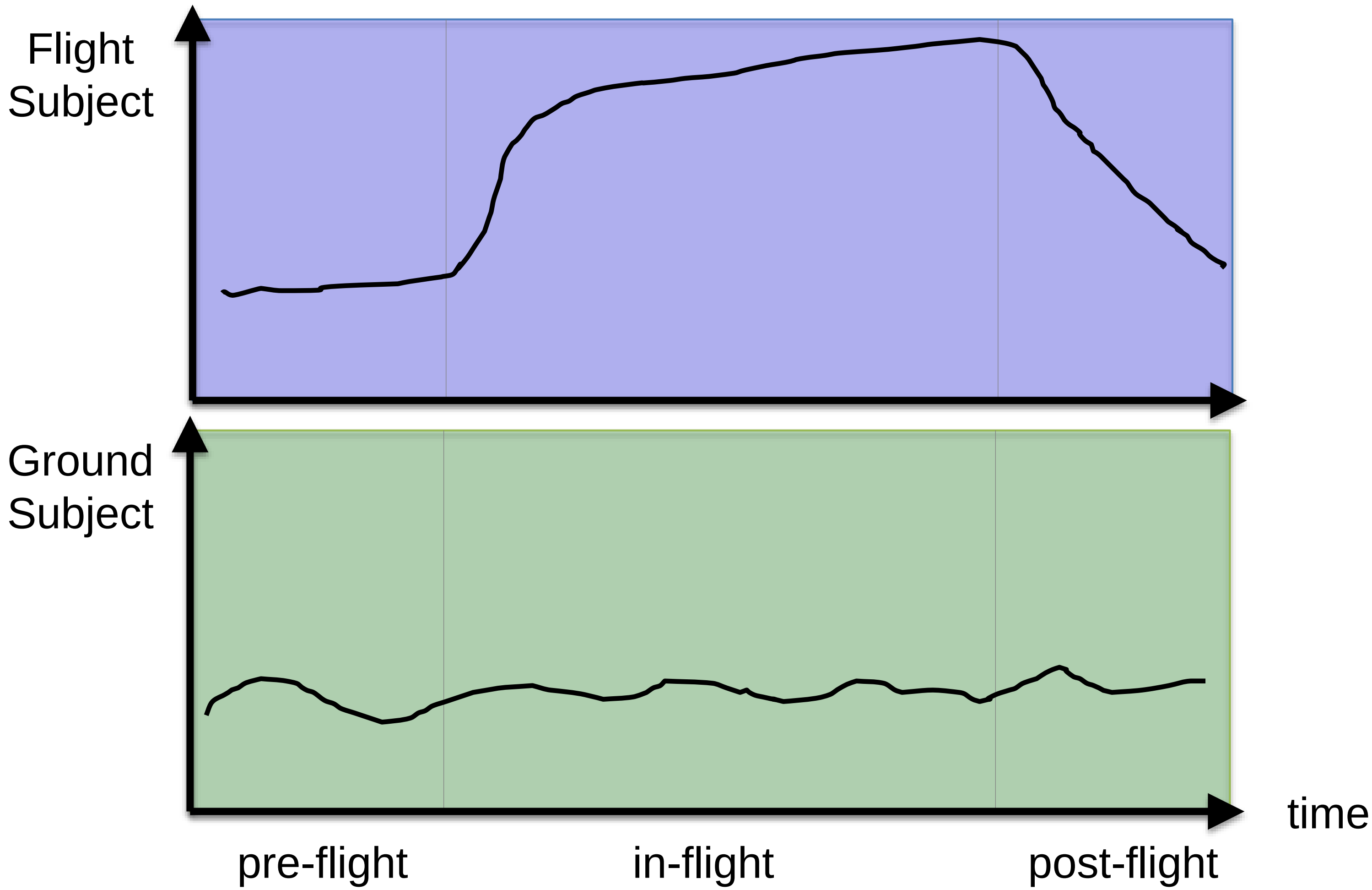
What is Omics?





Omics refers to the collective technologies used to explore the roles, relationships, and actions of the various types of molecules that make up the cells of an organism.

One Notion



Flight Subject
Ground Subject
time
pre-flight
in-flight
post-flight

NRA Solicitation

National Aeronautics and Space Administration
Johnson Space Center
Human Exploration and Operations Mission Directorate
Human Research Program
Houston, TX 77058

Human Exploration Research Opportunities (HERO)

Appendix D

Differential Effects on Homozygous Twin Astronauts Associated with Differences in Exposure to Spaceflight Factors

Response Period: July 30, 2013 – September 17, 2013
Proposals Due: September 17, 2013, 5 PM Eastern Time
Estimated Selection Announcement: January 2014

Appendix D - 1

"To capitalize on this unique opportunity,

NASA's Human Research Program (HRP) and the National Space Biomedical Research Institute (NSBRI) are initiating

a *pilot demonstration project focused on the use of integrated human -omic analyses* to

better understand the biomolecular responses to

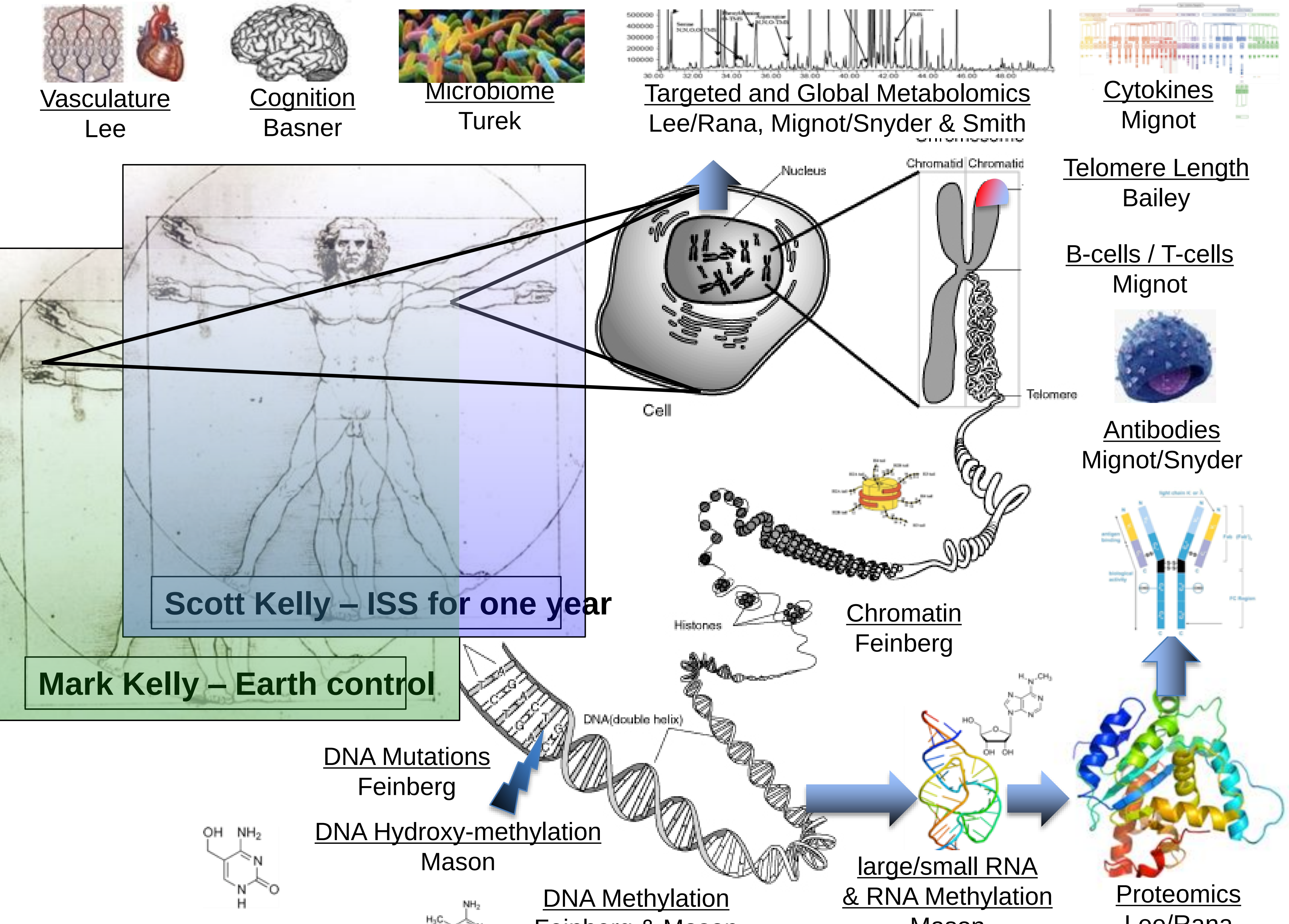
the physical,
physiological, and
environmental stressors

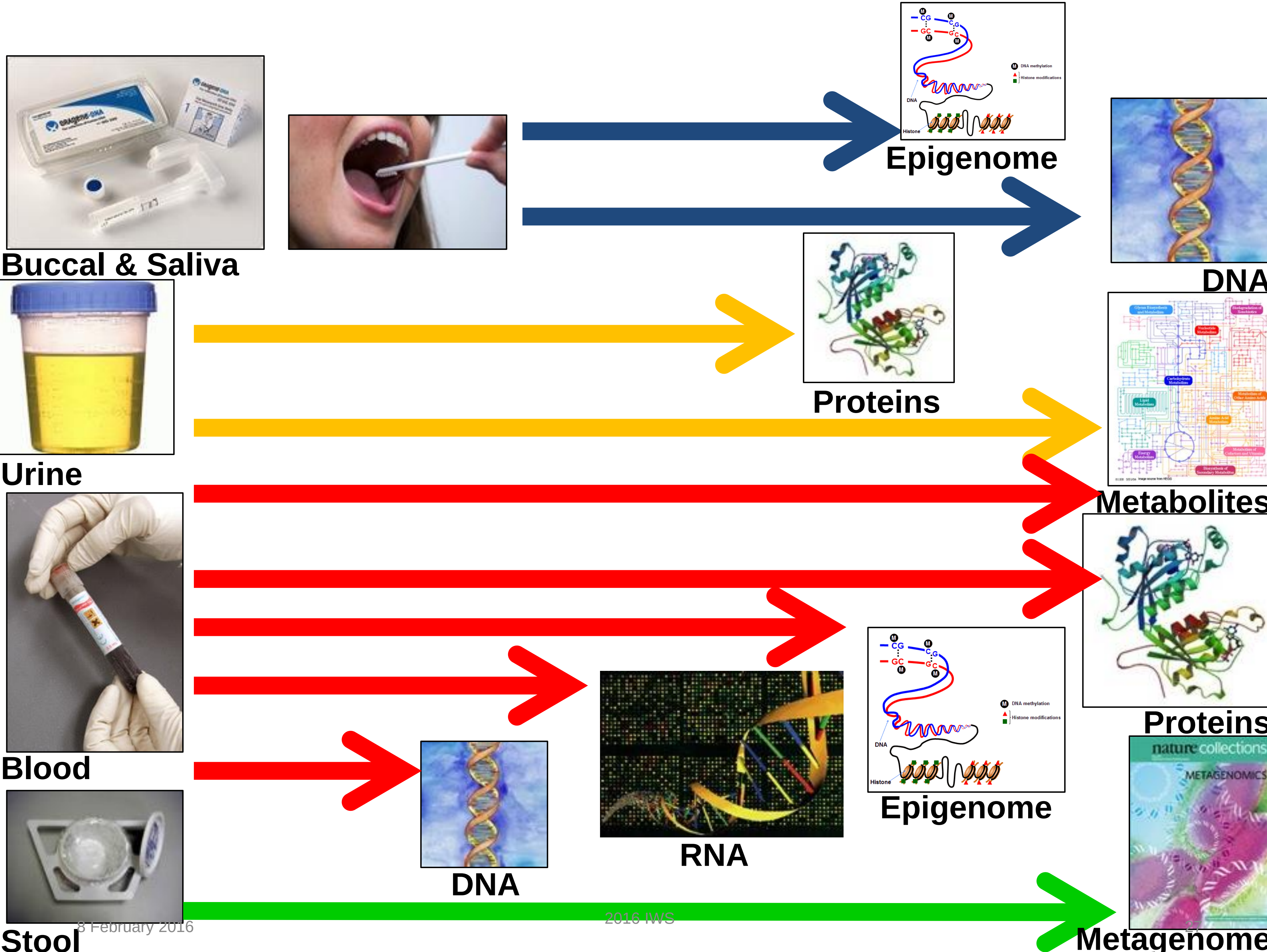
associated with spaceflight."

NRA Selections

Susan Bailey Colorado State University	Differential effects on telomeres and telomerase in twin astronauts associated with spaceflight
Andrew Feinberg Johns Hopkins University School of Medicine	Comprehensive whole genome analysis of differential epigenetic effects of space travel on monozygotic twins
Christopher Mason Weill Medical College of Cornell University	The Landscape of DNA and RNA Methylation Before, During, and After Human Space Travel
Scott Smith NASA Johnson Space Center	Biochemical Profile: Homozygous Twin control for a 12 month Space Flight Exposure
Emmanuel Mignot Stanford University School of Medicine	HERO Twin Astronaut Study Consortium (TASC): Immunome Changes in Space
Stuart Lee Wyle Laboratories	Metabolomic And Genomic Markers Of Atherosclerosis As Related To Oxidative Stress, Inflammation, And Vascular Function In Twin Astronauts
Brinda Rana University of California	Proteomic Assessment of Fluid Shifts and Association with Visual Impairment and Intracranial Pressure in Twin Astronauts
Mathias Basner University of Pennsylvania School of Medicine	HERO Twin Astronaut Study Consortium (TASC) Project: Cognition on Monozygotic Twin on Earth
Fred Turek Northwestern University	HERO Twin Astronaut Study Consortium (TASC) Project: Metagenomic Sequencing of the Bacteriome in GI Tract of Twin Astronauts
Michael Snyder Stanford University	HERO Twin Astronaut Study Consortium (TASC) Project: Longitudinal integrated multi-omics analysis of the biomolecular effects of space travel

http://www.nasa.gov/content/nasa-selects-10-proposals-to-explore-genetic-aspects-of-spaceflight/


Vasculature
Lee
Cognition
Basner
Microbiome
Turek
Targeted and Global Metabolomics
Lee/Rana, Mignot/Snyder & Smith
Cytokines
Mignot
Telomere Length
Bailey
B-cells / T-cells
Mignot
Antibodies
Mignot/Snyder
Nucleus
Chromatid
Chromatid
Telomere
Cell
Scott Kelly – ISS for one year
Mark Kelly – Earth control
Chromatin
Feinberg
Histones
DNA(double helix)
DNA Mutations
Feinberg
DNA Hydroxy-methylation
Mason
DNA Methylation
Feinberg & Mason
large/small RNA
& RNA Methylation
Mason
Proteomics
Lee/Rana


Epigenome
DNA methylation
Histone modifications
DNA
Histone
Buccal & Saliva
DNA
Proteins
Urine
Metabolites
Blood
Proteins
Epigenome
RNA
DNA
Stool
nature collections
METAGENOMICS
Metagenome

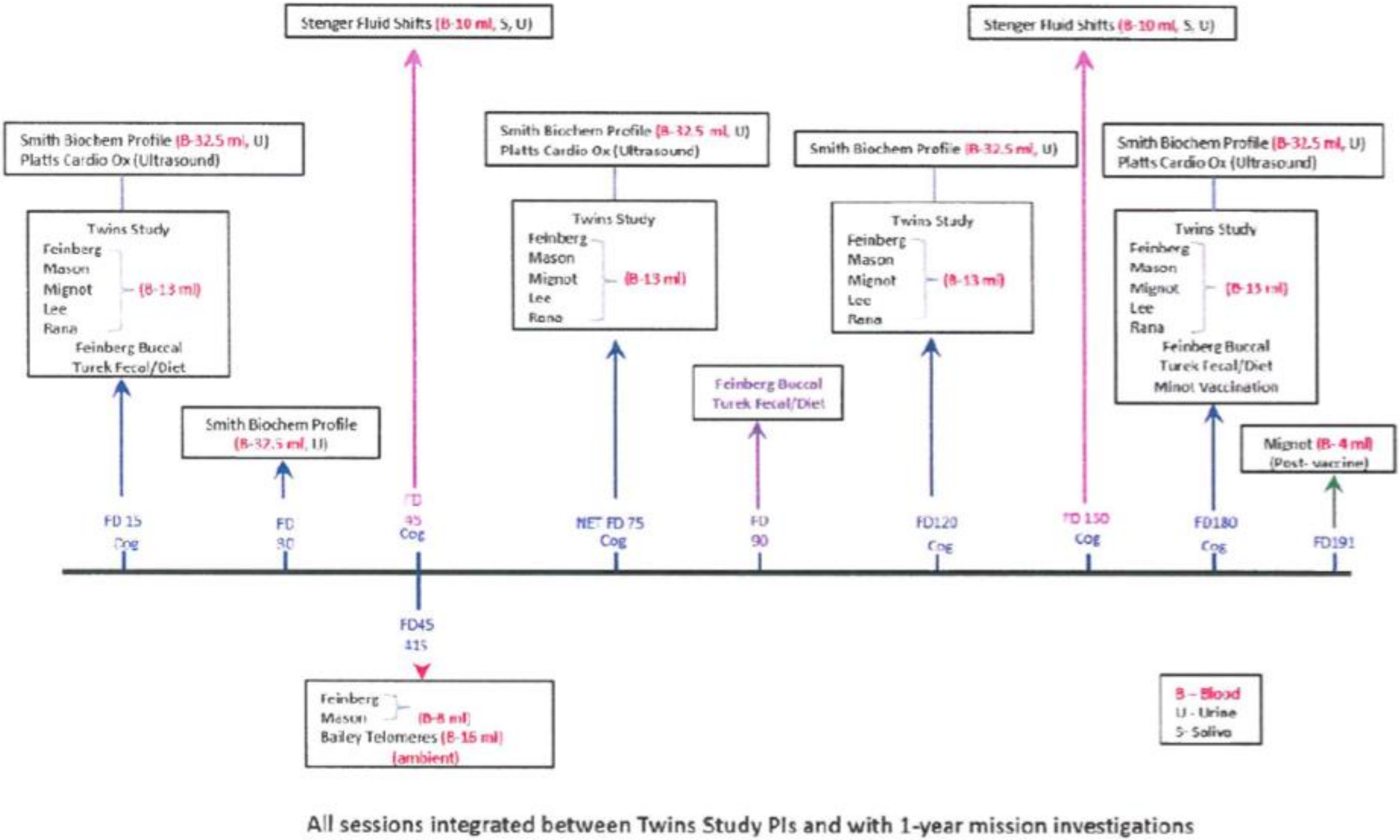
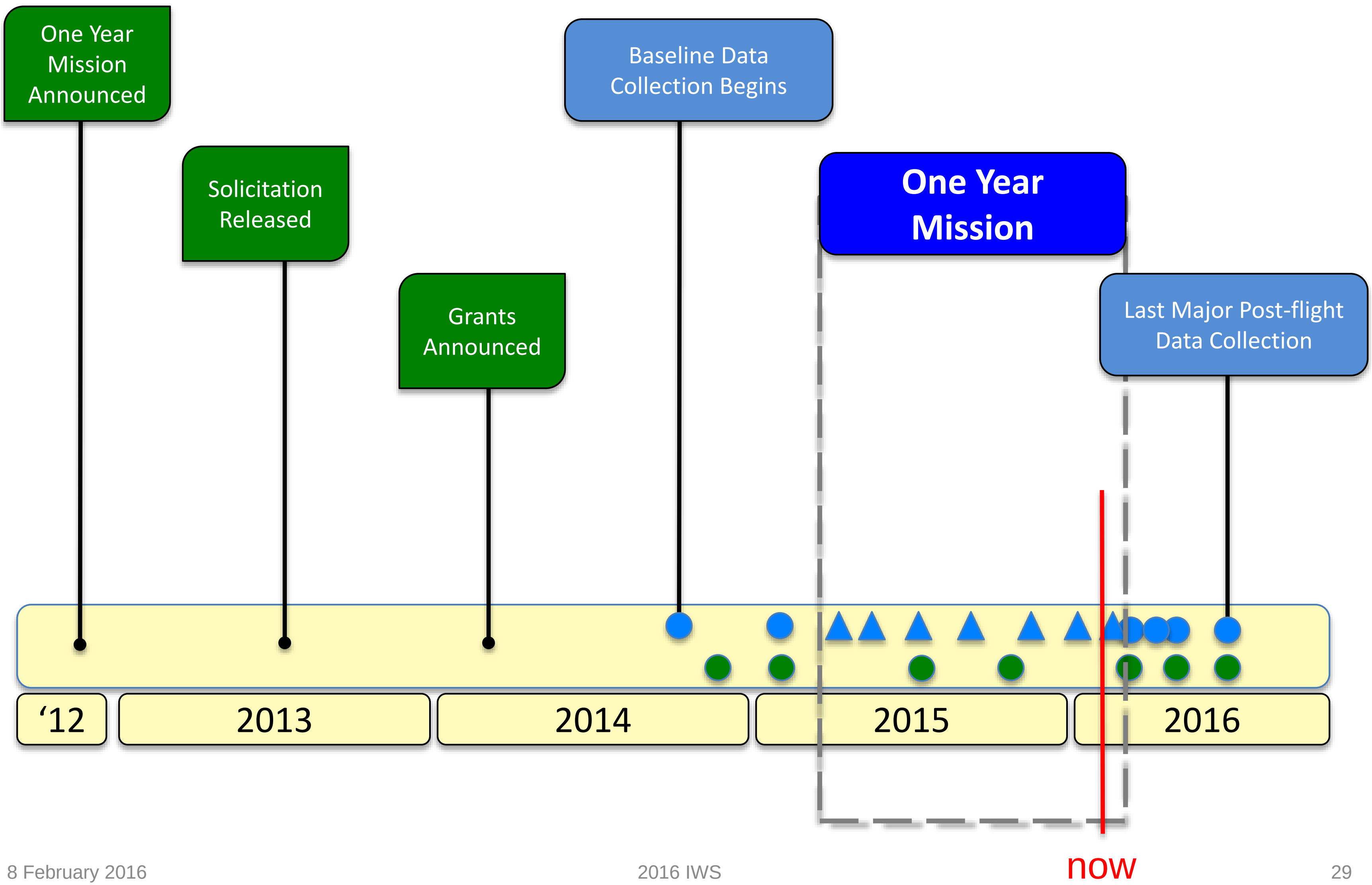


Figure 4 Integrated In-Flight Timeline – Flight Subject

Timeline



One Year Mission Announced
Solicitation Released
Grants Announced
Baseline Data Collection Begins
One Year Mission
Last Major Post-flight Data Collection
'12
2013
2014
2015
2016
now

Twins study progress

Launch Date			**3/27/15**									
Landing Date			**3/3/16**									
Subject	Location		NASA Date	Calendar Date		Actual Date	Subject	Location		NASA Date	Calendar Date	Actual Date
Flight	JSC		L-180	10/14/2014		10/16/14	Ground	JSC		GD-90	12/28/14	12/3/14
Flight	JSC		L-169 (Post Vac)	10/27/14		10/30/14	Ground	New York		GD-79* (Post-Vac)	1/8/15	12/13/14
Flight	JSC		L-60	1/28/15		1/15/15	Ground	JSC		GD-60/30	1/28/15	1/20/15
					Flight Day							
Flight	ISS	Frozen	FD 15	4/11/15	FD 15	4/10/15						
Flight	ISS	Frozen	FD NET 75	6/10/15	FD 75	6/9/15						
Flight	ISS	Ambient	FD 45	5/11/15	FD 77	6/11/15						
Flight	ISS	Frozen	FD 120	7/25/15	FD 123	7/27/15	Ground	Tucson		GD	August, 2015	7/30/15
Flight	ISS	Frozen	FD 180	9/23/15	FD 182	9/24/15	Ground	JSC		GD 180	9/23/15	10/1-2/15
Flight	ISS	Frozen	FD 191 (Post Vac)	10/4/15	FD 193	10/5/15	Ground	Tucson		GD 191 (Post Vac)	10/4/15	10/16/15
Flight	ISS	Ambient	**FD 271**	**12/22/15**								
Flight	ISS	Frozen	FD NET 263	12/15/15								
Flight	ISS	Frozen	FD 300	1/21/16								
Flight	ISS	Frozen	R-14	2/18/16								
Flight	ISS	Ambient	R-1	3/3/16								
Flight	JSC		R+0-3	3/4/16			Ground	JSC		GD+3-6	3/6/16	
Flight	JSC		R+30	4/2/16								
Flight	JSC		R+60	5/2/16			Ground	Tucson		GD+90	6/1/16	
Flight	JSC		R+180	8/30/16			Ground	Tucson		GD+180	8/30/16	
Flight	JSC		R+191 (Post Vac)	9/10/16			Ground	Tucson		GD+191 (Post Vac)	9/10/16	

Dates are for CPTs only

Dates are relative to launch and landing dates

Dates are proposed only and depend on subject availability and on-orbit operations schedule

Flight CPTs returned ambient via Soyuz, Dates shown are Soyuz return, Sample return to JSC approx 25 hrs post landing in Russia

Flight CPTs returned frozen may be stored at JSC until all in-flight samples are returned

In-flight CPTs are stored frozen, except ambient return. Frozen sample return is dependent on SpaceX vehicle return. Current SpaceX return dates:

SpaceX 8	1/3/16
SpaceX 9	3/21/16
SpaceX 10	6/10/16

Issues Associated with Omic Research

- **Research ethics**
  - ❖ The primary risks involved in genetic research are risks of social and psychological harm, rather than risks of physical injury
    - Could provoke anxiety and confusion about disease risk
    - Uncover unwanted information about heritage, ancestry, and family relationships
  - ❖ De-identification of genomic information
  - ❖ Information given to subjects
    - Individual genome sequence data?
    - Interpretation of the genome sequence and/or genetic counseling?
    - Option to decline to receive all or part of the results (Right Not to Know)?
  - ❖ Researcher's access to genomic information
  - ❖ Interim policy on genetic research JID 1800.4
  - ❖ NASA policy anticipated summer 2015
- **Medical care**
- **Occupational health**
- **Insurance (health, disability, life)**
- **Employment activity**

Conclusion

- **The Twins Study (Scott and Mark Kelly) is NASA's first foray into 21st-century omics research**
  - ❖ Built around Scott Kelly's one year mission
- **The Twins Study will examine**
  - ❖ Genome, telomeres, epigenome
  - ❖ Transcriptome and epitranscriptom
  - ❖ Proteome
  - ❖ Metabolome
  - ❖ Physiology
  - ❖ Cognition
  - ❖ Microbiome

- **NASA is addressing**
  - ❖ Protections for research participants
  - ❖ Use of data in medical care, occupational medicine, mission planning

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backup

A stunt?

No value in n = 1 omics study over time?

Resource

Cell

Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

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SUMMARY

Personalized medicine is expected to benefit from combining genomic information with regular monitoring of physiological states by multiple high-throughput methods. Here, we present an integrative personal omics profile (iPOP), an analysis that combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from a single individual over a 14 month period. Our iPOP analysis revealed various medical risks, including type 2 diabetes. It also uncovered extensive, dynamic changes in diverse molecular components and biological pathways across healthy and diseased conditions. Extremely high-coverage genomic and transcriptomic data, which provide the basis of our iPOP, revealed extensive heteroallelic changes during healthy and diseased states and an unexpected RNA editing mechanism. This study demonstrates that longitudinal iPOP can be used to interpret healthy and diseased states by connecting genomic information with additional dynamic omics activity.

INTRODUCTION

Personalized medicine aims to assess medical risks, monitor, diagnose and treat patients according to their specific genetic composition and molecular phenotype. The advent of genome sequencing and the analysis of physiological states has proven to be powerful (Cancer Genome Atlas Research Network, 2011). However, its implementation for the analysis of otherwise healthy individuals for estimation of disease risk and medical interpretation is less clear. Much of the genome is difficult to interpret and many complex diseases, such as diabetes, neurological disorders and cancer, likely involve a large number of different genes and biological pathways (Ashley et al., 2010; Grayson et al., 2011; Li et al., 2011), as well as environmental contributors that can be difficult to assess. As such, the combination of genomic information along with a detailed molecular analysis of samples will be important for predicting, diagnosing and treating diseases as well as for understanding the onset, progression, and prevalence of disease states (Snyder et al., 2009).

Presently, healthy and diseased states are typically followed using a limited number of assays that analyze a small number of markers of distinct types. With the advancement of many new technologies, it is now possible to analyze upward of 10^5 molecular constituents. For example, DNA microarrays have allowed the subcategorization of lymphomas and gliomas

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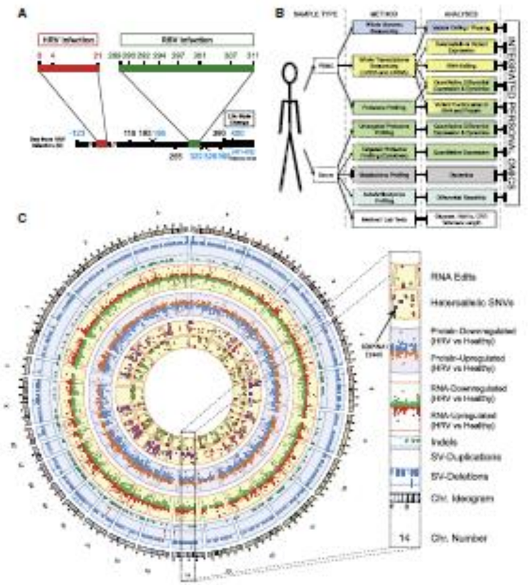

Figure 1. Summary of Study

(A) Time course summary. The subject was monitored for a total of 726 days, during which there were two infections (red bar, HRV; green bar, RSV). The black bar indicates the period when the subject: (1) increased exercise, (2) ingested 81 mg of acetylsalicylic acid and ibuprofen tablets each day (the latter only during the first 6 weeks of this period), and (3) substantially reduced sugar intake. Blue numbers indicate tested time points.
(B) iPOP experimental design indicating the tissues and analyses involved in this study.
(C) Circos (Krzywinski et al., 2009) plot summarizing iPOP. From outer to inner rings: chromosome ideogram; genomic data (pale blue ring), structural variants > 50 bp (deletions [blue tiles], duplications [red tiles]), indels (green triangles); transcriptomic data (yellow ring), expression ratio of HRV infection to healthy states; proteomic data (light purple ring), ratio of protein levels during HRV infection to healthy states; transcriptomic data (yellow ring), differential heteroallelic expression ratio of alternative allele to reference allele for missense and synonymous variants (purple dots) and candidate RNA missense and synonymous edits (red triangles, purple dots, orange triangles and green dots, respectively).
See also Figure S1.

WGS-Based Disease Risk Evaluation

We identified variants likely to be associated with increased susceptibility to disease (Dewey et al., 2011). The list of high confidence SNVs and indels was analyzed for rare alleles (<5% of the major allele frequency in Europeans) and for changes in genes with known Mendelian disease phenotypes (data summarized in Table 2), revealing that 51 and 4 of the rare coding SNV and indels, respectively, in genes present in OMIM are predicted to lead to loss-of-function (Table S2A). This list of genes was further examined for medical relevance (Table S2A; example alleles are summarized in Figure 2A), and 11 were validated by Sanger sequencing. High interest genes include: (1) a mutation (E366K) in the *SERPINA1* gene previously known in the subject, (2) a damaging mutation in *TERT*, associated with acquired aplastic anemia (Yamaguchi et al., 2005), and (3) variants associated with hypertriglyceridemia and diabetes, such as *GCKR*

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Where Does Omics Fit In?